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TITLE: Method of extending the plasma half-life of vascular endothelial cell growth factor

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In a preferred embodiment, the heparin-binding protein is HGF, more preferably native huHGF or a functional derivative or inhibitor thereof. HGF variants are, for example, disclosed in U.S. Pat, No. 5,316,921 and U.S. Pat. No. 5,328,837. As it has been shown that the receptor binding domain is contained within the finger and Kringle 1 (K1) regions of the native huHGF molecule, in addition to the heparin-binding site(s), the HGF variants preferably contain a functional finger and K1 region. In another preferred group of HGF variants a functional Kringle 2 (K2) region is additionally present. We have experimentally found that huHGF variants composed of the finger, K1 and K2 domains of native huHGF retain the ability to bind heparin, i.e. contain at least one heparin-binding site. Single-chain HGF variants, which are resistant to proteolytic cleavage by trypsin-like proteases at the one-chain to two-chain cleavage site between Arg494 and Val495 of native huHGF are able to bind the HGF receptor but substantially lack biological activity (i.e. they are HGF inhibitors). Such variants preferably contain single or multiple amino acid substitutions, insertions and/or deletions at or adjacent to amino acid positions 493, 494, 495 and 496 of the native huHGF amino acid

sequence. A preferred alteration is the replacement of arginine at amino acid position 494 with any other amino acid, preferably glutamic acid, aspartic acid or alanine. Alterations that potentially increase the receptor binding capacity of native huHGF are, for example, in the amino acid region corresponding to a potential serine protease active site. This region includes amino acids Q534, Y673 and V692 in the native huHGF amino acid sequence. The replacement of these amino acids with any other amino acid, and preferably with amino acids of different size and/or polarity is believed to further improve the receptor binding properties of huHGF.